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Reply: An Incomplete Story

We thank Dr. Reiffel for his interest in our paper (1). Beta-blockers reduced mortality in landmark, placebo-controlled trials of heart failure with a reduced left ventricular ejection fraction only for those in sinus rhythm rather than atrial fibrillation (AF), despite use of similar beta-blocker formulations and doses (84% of target) and similar heart rate reductions (1). For patients in AF, neither baseline nor follow-up ventricular rate was associated with beta-blocker benefit, nor have trials comparing rate control intensity shown important differences in outcome, although slower rates may be associated with a worse prognosis for patients with heart failure (2).

Physiologically, slowing heart rate increases pulse and systolic blood pressures. Multivariable analyses investigating interactions amongst heart rate, rhythm, and beta-blockers were adjusted for systolic pressure. AF with ventricular rate <70 beats/min was associated with a 6 mm Hg higher systolic pressure than when >90 beats/min but higher pressure was not associated with a better prognosis.

Data on individual angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers or their doses were not collected but the proportion prescribed (about 95%) these was similar regardless of heart rhythm. Analyses correcting for use of mineralocorticoid antagonists and digoxin did not affect our conclusions (see Online Table 3 in [1]).

Observational studies of digoxin are prone to prescribing and other biases, even when propensity-adjusted, and should not be used to assess treatment responses. Randomized trials show no impact of digoxin on mortality in sinus rhythm but do show reductions in hospitalization (3). Prospective trials of cardiac glycosides in patients with AF are underway (4).

References

- 1) D. Kotecha, M.D. Flather, D.G. Altman, et al., for the Beta-Blockers in Heart Failure Collaborative Group Heart rate and rhythm and the benefit of beta-blockers in patients with heart failure. *J Am Coll Cardiol*, 69 (2017), pp. 2885-2896.
- 2) D. Cullington, K.M. Goode, J. Zhang, J.G. Cleland, A.L. Clark Is heart rate important for patients with heart failure in atrial fibrillation? *J Am Coll Cardiol HF*, 2 (2014), pp. 213-220.
- 3) O.J. Ziff, D.A. Lane, M. Samra, et al. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. *BMJ*, 351 (2015), Article h4451.
- 4) D. Kotecha, M. Calvert, J.J. Deeks, et al. A review of rate control in atrial fibrillation, and the rationale and protocol for the RATE-AF trial. *BMJ Open*, 7 (2017), Article e015099.